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BJS, 2021, 1–3
DOI: 10.1093/bjs/znab178
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# Exploring Koch's postulate for SARS-CoV-2-induced acute pancreatitis: is it all about the ACE?

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The pathogenesis of SARS-CoV-2 infection depends on the ability of the virus to bind to the angiotensin-converting enzyme 2 (ACE2) receptor-primed cellular transmembrane serine protease 2 (TMPRSS2) receptor to facilitate entry into cells. Although respiratory symptoms are the most common presentation, gastrointestinal symptoms are frequent[1]. Endoscopic biopsies have detected the SARS-CoV-2 virus in the oesophagus, stomach, duodenum, and rectum, and ACE-2 receptor is expressed throughout the gastrointestinal tract, including the pancreas[2]. The mRNA levels of ACE2 receptors in exocrine cells and islet cells of pancreas were noted to be higher than in lung[3], which raised the question of whether SARS-CoV-2 infection can cause acute pancreatitis. Several published reports of concomitant SARS-CoV-2 infection and acute pancreatitis revealed a spectrum of signs consistent with acute pancreatitis, including hyperglycaemia, unusual patterns of pancreatitis without necrosis on imaging, a predilection for younger overweight or obese patients and black and Hispanic patients with liver steatosis, and an exaggerated systematic inflammatory response[4]. In the majority of reported events, the aetiology of acute pancreatitis was idiopathic. The early observations have raised some important questions.

Although the data suggest a temporal and causal relationship between SARS-CoV-2 and acute pancreatitis, this has been difficult to prove from short case series. The COVID PAN (COVID Pancreatitis) study[5] of 1777 patients with acute pancreatitis predominantly from Western Europe included 149 patients who also had SARS-CoV-2 infection. Support for the temporal relationship between acute pancreatitis and SARS-CoV-2 infections came from the finding that 73 per cent of patients with a positive reverse transcriptase–PCR swab within 72 h of admission already had acute pancreatitis.

Data that support a possible causal relationship between SARS-CoV-2 infection and acute pancreatitis come from the experimental finding that ACE2 and TMPRSS2 are co-expressed in pancreatic ductal cells (*Fig. 1*) to enable viral entry[6], and infection of human organoid pluripotent stem cell-derived pancreatic cultures containing endocrine and exocrine cells by SARS-CoV-2 has confirmed infectivity and raised levels of CXCL12, a key inflammatory cytokine known to cause ribosomal damage and pancreatic dysfunction[7]. In cultured human β-cells that do not co-express ACE2 and TMPRSS2, but do express viral entry proteins (neuropilin 1), SARS-CoV-2 has been shown to replicate and cause morphological, transcriptional, and functional changes to the cells as well as impaired glucose-stimulated insulin secretion[6]. In addition, autopsy examination of pancreases from four patients with SARS-CoV-2 infection detected SARS-CoV-2 nucleocapsid protein in pancreatic exocrine cells and β-cells, and in close proximity to islets in all four patients. One patient presented with a raised serum lipase level, raising the possibility of asymptomatic acute pancreatitis[6].

The available data currently fulfil two of the four Koch postulates, the first being that SARS-CoV-2 was identified in the pancreas of infected patients, and second that SARS-CoV-2 can infect exocrine and endocrine cells *ex vivo* and *in vivo*. However, the remaining two of Koch's postulates, including the inoculation of samples of SARS-CoV-2 obtained from pure culture into animal or human subjects to reproduce the disease, and isolation of virus from those inoculated subjects, may not be fulfilled for ethical reasons. There is not yet absolute proof of a causal it is important to remember that many bacteria and viruses fail to fulfil Koch's postulates, yet the agents are widely accepted as the cause of disease (such as Dengue virus) with which they are associated.

The COVID PAN study[5] suggested that acute pancreatitis was more severe when associated with SARS-CoV-2 infection, and patients were at greater risk of persistent organ failure, local pancreatic complications, and death. In a recent series of patients under intensive care with SARS-CoV-2 infection, acute pancreatitis was detected in 12.6 per cent of patients in the ICU, and one-third of critically ill patients with SARS-CoV-2 infection developed concomitant acute pancreatitis[8]. Hyperlipasaemia (over the 3 times upper normal limit) often with a raised D-dimer level appear to be frequent in patients with SARS-CoV-2, and predict the need for mechanical ventilation and death[9]. Although it

**Received:** March 07, 2021. **Accepted:** April 23, 2021

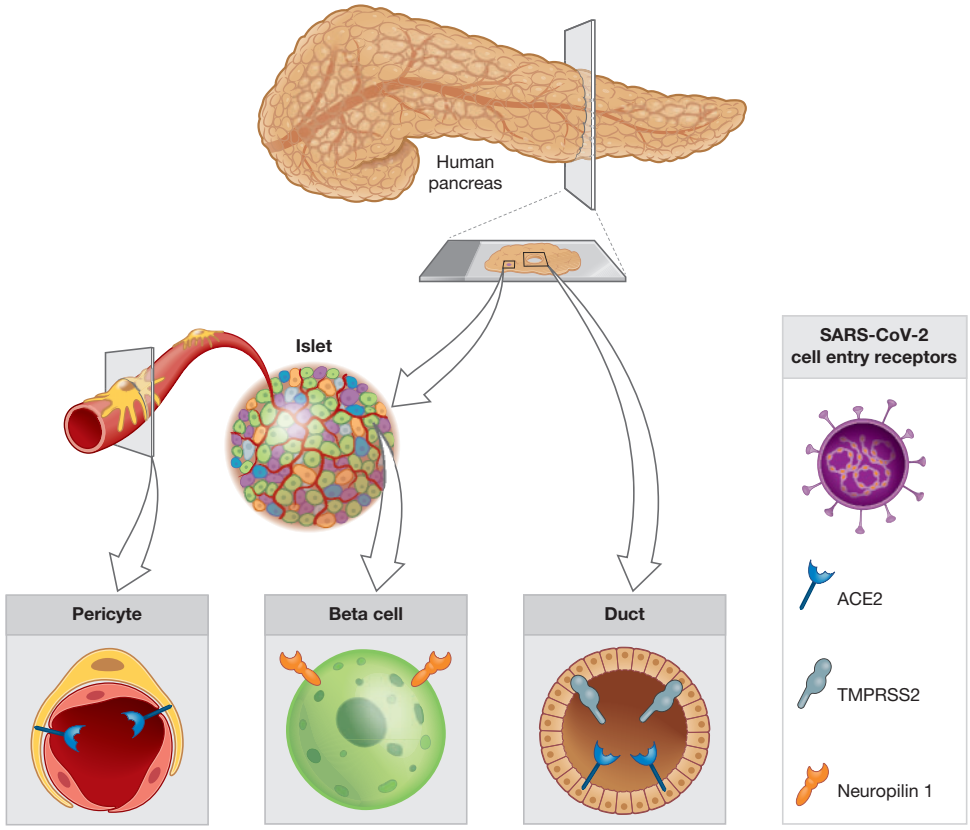


**Fig. 1 SARS-CoV-2 cell entry receptors expressed on pancreas cells.**

is possible that SARS-CoV-2 infection directly increases the risk of organ failure and mortality independent of acute pancreatitis, endothelitis and the prothrombotic state seen with SARS-CoV-2 infection and splanchnic vasoconstriction, often seen in severe acute pancreatitis, may have contributed to a spectrum ranging from subclinical pancreatitis with hyperlipasaemia to severe acute pancreatitis. Although clinical evidence indicates that acute pancreatitis is more severe when associated with SARS-CoV-2 infection, experimental evidence of more severe pancreatic injury is lacking.

The Adaptive COVID-19 Treatment Trial of remdesivir and the UK RECOVERY study of dexamethasone showed decreased recovery time and mortality in hospitalized adults with SARS-CoV-2 infection. As yet, there is no evidence that such drugs decrease the severity of acute pancreatitis or improve outcomes. In the laboratory setting, remdesivir treatment of pancreatic islets infected with SARS-CoV-2 resulted in suppression of SARS-CoV-2 replication and no detectable virus in the supernatant of islets[6]. Dexamethasone reduces oedema and apoptosis in animal models of severe acute pancreatitis. Camostat mesylate, a serine protease inhibitor used to treat acute pancreatitis in Japan, is active against TMPRSS2, inhibits SARS-CoV-2 infection in human lung cells, and is currently being evaluated in a clinical trial to see if it reduces SARS-CoV-2 disease severity[10]. These drugs have the potential to treat both SARS-CoV-2 infection and acute pancreatitis, but clinical evidence is awaited.

The COVID PAN study and laboratory investigations have increased understanding of acute pancreatitis associated with SARS-CoV-2 infection. Koch's postulates would need to be fulfilled to provide definitive proof that SARS-CoV-2 causes acute pancreatitis, but the accumulating data appear to support this. The low prevalence of acute pancreatitis (0.27 per cent) means that large population studies will be required to confirm the COVID PAN findings, and demonstrate a plausible temporal relationship between acute pancreatitis and SARS-CoV-2 infection. Future studies will need to demonstrate the replication cycle of SARS-CoV-2 in acinar cells, and the development of pancreatic inflammation and injury, but this will require human pancreas samples.

*Conflict of interest*. The author declares no conflict of interest.

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